L35 ANSWER 108 OF 272 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:674828 HCAPLUS Full-text
DOCUMENT NUMBER: 129:343716
TITLE: Method for phosphorylation of cyclosporins
INVENTOR(S): Oki, Tadaki; Imano, Kiyotaka; Seto, Takashi; Ueda, Toshihiro
PATENT ASSIGNEE(S): Nippon Shinyaku Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 8 pp.

CODEN: JKXXAF

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
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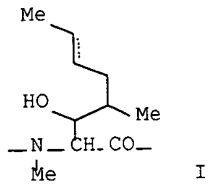
PRIORITY APPLN. INFO.:			JP 1997-88311	19970407

OTHER SOURCE(S): CASREACT 129:343716
GI



I

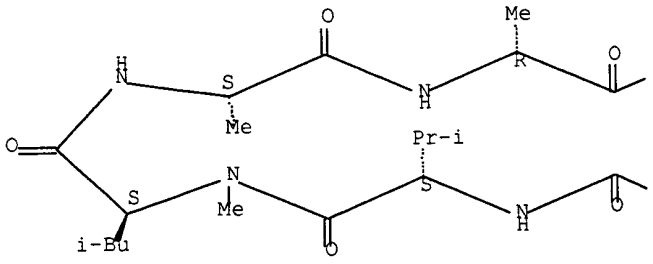
AB The alc. hydroxy group in the side chain (I) of cyclosporins is phosphorylated by activation of the hydroxy group with a base to the alkoxide and then reaction with a phosphorylating agent to give cyclosporin phosphate esters. The base capable of activating the alc. hydroxy group is Grignard reagent, alkali metal amide, and alkyllithium. Also claimed is an immunosuppressant containing cyclosporin phosphate esters. This process provides water-soluble cyclosporin phosphate esters, in particular cyclosporin A phosphate ester. Thus, 2.5 g cyclosporin A was dissolved in THF, treated with a 2M THF solution of Me3COMgCl (12.5 mL) at room temperature, and stirred for 15 min, followed by adding 1.34 mL adding di-Me chlorophosphate, (MeO)2P(:O)Cl, and the resulting mixture was stirred for 4 h to give cyclosporin A dimethylphosphate ester. The latter ester (100 mg) was dissolved in MeCN and treated with 220 μL thioanisole, 200 μL chlorotrimethylsilane, and 130 mg LiI under ice-cooling, and the resulting mixture was stirred at 0° for 25 h and treated with MeOH to give, after reversed phase chromatog. (LiChroprep RP-18), 71.8% cyclosporin A phosphate ester.

IT **215385-30-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); **PREP (Preparation)**; RACT (Reactant or reagent)
(method for phosphorylation of cyclosporins and preparation of cyclosporin phosphate esters for immunosuppressants)

RN 215385-30-1 HCAPLUS
CN Cyclosporin A, dimethyl phosphate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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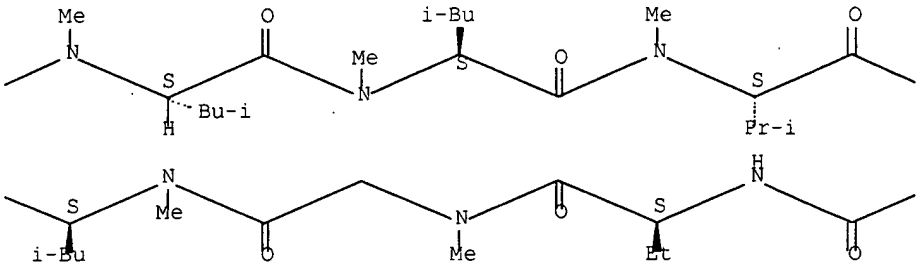
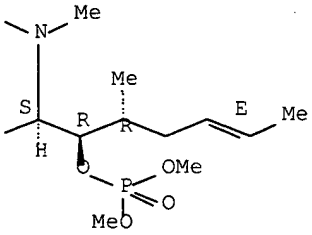


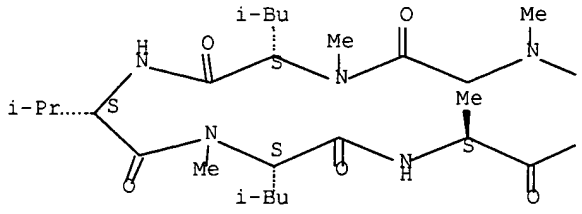
PAGE 1-C



IT **173946-64-0P 174062-41-0P 215385-29-8P**,
Cyclosporin A methylphosphate ester
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(method for phosphorylation of cyclosporins and preparation of cyclosporin phosphate esters for immunosuppressants)
RN 173946-64-0 HCAPLUS
CN Cyclosporin A, dihydrogen phosphate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A



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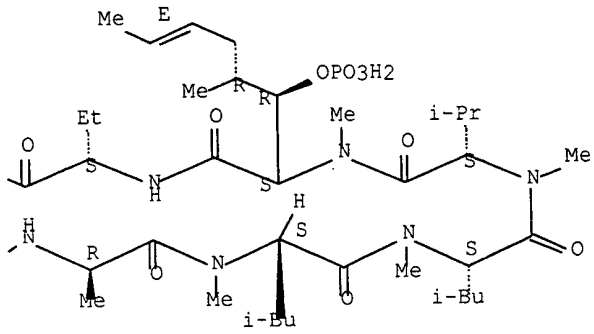


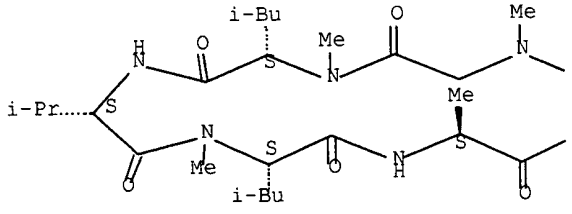
RN 174062-41-0 HCAPLUS
CN Cyclosporin A, dihydrogen phosphate (ester), disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.

PAGE 1-A

2 Na

PAGE 1-B



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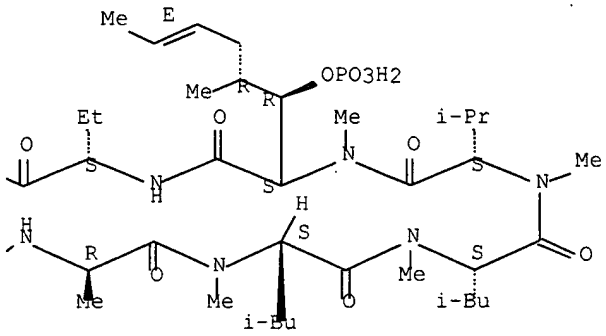
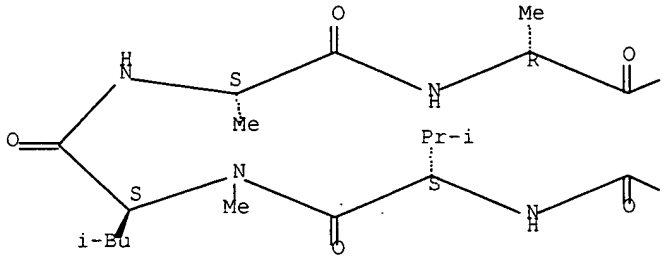


RN 215385-29-8 HCAPLUS
CN Cyclosporin A, methyl hydrogen phosphate (ester) (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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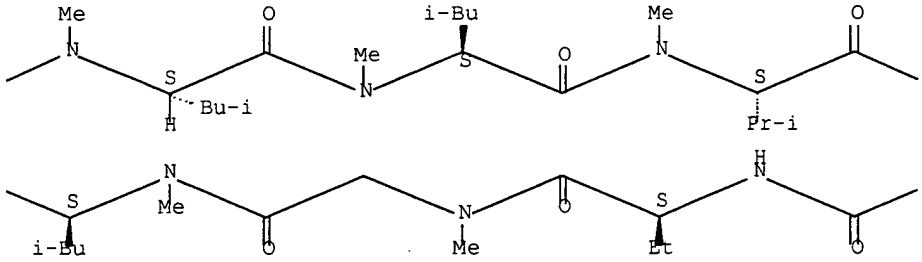

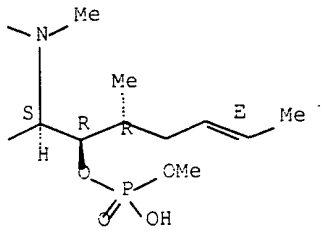
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